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| EXAMINER | |
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | 15 |

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Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/381,903 | KAHLERT ET AL. | |
| | Examiner | Art Unit | |
| | Margaret E Jamroz | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *8/17/01, 10/22/01, and 1/18/02* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *10 and 12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Art Unit location and the examiner of your application in the PTO have changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Megan Jamroz, Art Unit 1644, Technology Center 1600.

2. Applicant's amendments, filed 1/18/02, 10/22/01, and 4/17/01 (Paper Nos. 5, 11, and 14), are acknowledged.

Claims 1-14 are pending.

Applicant's election with traverse of Group I (Claims 1-9 and 11) in Paper No. 14 is acknowledged. The traversal is on the ground(s) that a product under PCT rules should be examined with its first process of making and first process of using, that all of the subject claims do relate to a single inventive concept, and that the Office has not proved a burden of search. This is not found persuasive because if the product does not contribute a special technical feature over the prior art, it is correct to maintain the restriction between the product and methods of making and/or using. In the instant case, the claims do not define a contribution of a special technical feature over the prior art according to 37 CFR 1.475 (see MPEP 1850). The restriction of Groups II and III is maintained as they relate to a method for making the allergens and a method of using the allergens are, therefore, not linked to form a single general inventive concept.

The requirement is still deemed proper and is therefore made FINAL.

Claims 10 and 12-14 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to non-elected inventions.

Claims 1-9 and 11 are under consideration in the instant application.

3. Applicant's IDS, filed 06-2000 (Paper No. 6), is acknowledged, however, the references for the citations crossed out were not found in the priority documents or a translation was not provided. Applicant is invited to produce such documents.

4. Applicant should amend the first line of the specification (37 CFR 1.78) to indicate priority is claimed under 35 U.S.C. 371 to PCT/EP98/01507.

5. The following guidelines illustrate the preferred layout and content for patent applications. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

The following order or arrangement is preferred in framing the specification and, except for the reference to the drawings, each of the lettered items should appear in upper case, without underling or bold type, as section headings. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) Title of the Invention.

(b) Cross-Reference to Related Applications.

(c) Statement Regarding Federally Sponsored Research or Development.

(d) Reference to a "Sequence Listing," a table, or a computer program listing appendix submitted on compact disc (see 37 CFR 1.52(e)(5)).

(e) Background of the Invention.

1. Field of the Invention.
2. Description of the Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) Brief Summary of the Invention.

(g) Brief Description of the Several Views of the Drawing(s).

(h) Detailed Description of the Invention.

(i) Claim or Claims (commencing on a separate sheet).

(j) Abstract of the Disclosure (commencing on a separate sheet).

(k) Drawings.

(l) Sequence Listing, if on paper (see 37 CFR 1.821-1.825).

6. New formal drawings are required in this application because applicant has not provided a copy of the figures on separate sheets of paper. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the Patent and Trademark Office no longer prepares new drawings.

Applicant is reminded that formal drawings do not include titles or legends. Further, applicant is required to amend the specification to include a Brief Description of the Drawings. Applicant is notified that Figures 7-10 are **not** figures and should be incorporated into the specification as tables.

Applicant is required to submit acceptable drawings within the time period set in the Office action. See 37 CFR 1.85(a). Failure to take corrective action within the set period will result in **ABANDONMENT** of the application. The objection to the drawings will not be held in abeyance.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. Claim 9 is objected to under 37 CFR 1.812(d) for failing to recite the SEQ ID NOS for the polypeptides. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-9 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. The "allergens, "salts" and "solvates" recited in claims 1-9 should be changed to a singular format; otherwise, the claims as written would recite a mixture.

12. Claim 1 is indefinite and ambiguous because it is not clear how the modification is to occur. Further, there is no structural or functional definition as to the allergen.

13. Claim 2 is indefinite and ambiguous because it is not clear how the modification is to occur, and it is ambiguous as to what groups 1-6 are as they are not defined by the specification or the claims.

14. Claim 9 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of ..." with the use of the conjunction "and". See MPEP 706.03(Y).

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claims 1-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for SEQ ID NOS: 88-93 (i.e. modified Phl p 5b) and pharmaceutical compositions thereof for *in vitro* diagnosis of type I allergies to SEQ ID NO: 87 (Phl p 5b) and *in vivo* hyposensitization to modified SEQ ID NO: 87, does not reasonably provide enablement for any other modified recombinant allergen, any other modified recombinant allergen of any group wherein at least one of regions 16-42, 135-149, and 180-206, or a combination thereof, are not modified, or any pharmaceutical composition thereof for any *in vitro* diagnosis of type I allergies or any *in vivo* use. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims without an undue amount of experimentation.

(A) Applicant discloses 6 "groups" of allergens, but does not disclose a reference which teaches structural and functional characteristics of each group on page 1, paragraph 2. Applicant further discloses main allergens groups 1 and 5 taught in the references incorporated in the instant specification (i.e. Liebers et al. Clin. Exper. Allergy, 1996, 26: 494-516; Vrtala et al. J. Immunology 1993, 151: 4773-4781; and Bufe et al. FEBS Lett. 1995; 263: 6-12) on page 1, paragraph 2. Applicant describes allergens with specific amino acid regions which are not to be modified, however, applicant does not disclose a specific SEQ ID NO. Sequences of polypeptides differ between laboratories, and the sequence of one protein in one laboratory may differ from the sequence of another protein from a different laboratory even though they have the same name, therefore, one skilled in the art would not be able to determine whether positions 16-42, 135-149 and 180-206 are the same residues as another modified allergen from the same or different "group".

In the absence of specific definitions of the 6 different groups, it is impossible to determine what type of allergens are in each group, where the substitution occur, or do not occur; therefore, applicant has not taught how to make the claimed invention.

The incorporation of essential material in the specification by reference to a foreign application or patent, or **to a publication is improper**. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). "Essential

material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112).

The attempt to incorporate subject matter into this application by reference to Liebers et al. (Clin. Exper. Allergy, 1996, 26: 494-516); Vrtala et al. (J. Immunology 1993, 151: 4773-4781); and Bufe et al. (FEBS Lett. 1995; 263: 6-12) is improper because an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below.

Groups 1 and 5 taught by Liebers et al. (Clin. Exper. Allergy, 1996, 26: 494-516); Vrtala et al. (J. Immunology 1993, 151: 4773-4781); and Bufe et al. (FEBS Lett. 1995; 263: 6-12) is essential for prosecution of the instant application because the positions of the amino acid residues to be mutated cannot be determined in the absence of the proteins in each group. Further one skilled in the art would not be apprised as to the classification of allergens into the 6 "groups". Applicant should amend the specification to include the identification of groups 1-6 taught by Liebers et al. (Clin. Exper. Allergy, 1996, 26: 494-516); Vrtala et al. (J. Immunology 1993, 151: 4773-4781); and Bufe et al. (FEBS Lett. 1995; 263: 6-12).

(B) Further, applicant is not enabled for

(a) any modified recombinant allergen for *in vitro* diagnosis of type I allergies,

(b) any other modified recombinant allergen for *in vivo* therapeutic use.

(a) any sequence of any allergen other than SEQ ID NO: 87 (unmodified) or SEQ ID NOS: 88-93 (modified), or

(c) any other modified recombinant allergen from any group wherein the allergens are from any group and wherein said allergens are not modified at regions 16-42, 135-149, and 180-206, either alone or in combination, or

(d) any pharmaceutical composition thereof for *in vivo* theraeutic use.

The genus encompasses every allergen which has been modified in an unspecified way wherein such allergens have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes.

However, the present specification fails to provide sufficient disclosure of such allergens that maintain the structural and functional properties of the *Phl p* Vb set forth in SEQ ID NOS: 87-93. The specification does not provide sufficient guidance as to which of the amino acids may be changed while "modified recombinant allergen" structural or functional activity and specificity is retained.

Applicant has not taught how to make modifications to the unlimited number of allergens recited in the claims, where the modifications are to occur, or indeed, to what extent deletions of regions can occur in addition to further modifications by substitutions or additions, while maintaining structural and functional characteristics as claimed. Consequently, applicant has not taught how to make modifications in the unlimited number of allergens and use said modified antigenssuch that reactivity with IgE antibodies is eliminated or reduced and that the dominant T cell-reactive regions (i.e. capable of generating an antibody response) of the allergens are not altered by genetic manipulation. Therefore, applicant is not enabled to make and/or use the unlimited number of modified allergens for *in vitro* or *in vivo* use.

Therefore, without sufficient guidance to the large number of modified recombinant allergen to which antibodies would generated; there is insufficient guidance and direction as to make and use modified allergen-specific antibodies wherein the antibodies thereof bind any allergen comprising a recombinantly modified amino acid sequence other than the *Phl p* Vb allergens set forth in SEQ ID NOS: 87-93.

Coleman et al. (Research in Immunology, 1994; 145(1): 33-36) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza et al. (Journal of Protein Chemistry, Vol. 11, No. 5, 1992, pages 433-444) teaches single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Futher, Lederman et al. (Molecular Immunology 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li et al. (PNAS 77: 3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).

It is known in the art peptide therapy of allergies is highly unpredictable. Cao et al. (Allergy 1995 ; 50(suppl 25) : 37-44) teach that "some of the major allergens, particularly pollen allergens, contain a number of T cell epitopes and that allergic individuals differ with respect to their recognition of these epitopes, the success of this approach in presensitized individuals is difficult to predict", and despite progress in recombinant technology, application of peptide therapy is "at its infancy" (see page 42 in particular). Further, "taking into account the complexity of the allergic conditions, it is naïve to expect that one form of {peptide} immunotherapy would be effective in the treatmennt of allergies. For certain allergies (such as ragweed or grass?), protocols would involve a battery of [peptides] to target the polyclonal populations of T cells" (see bottom of page 42, right column, and top of page 43, left column in particular).

It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Applicant is relying upon certain biological activities and the disclosure of a limited representative number of species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated proteins having an unlimited number of amino acids which can be modified (conservatively or not) encompassed by the claimed invention other than "allergens set forth by SEQ ID NOS: 88-93" would be expected to have greater differences in their activities.

Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain binding or functional aspects of the modified allergens, and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

In re Fisher, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to function modified recombinant allergens with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

17. Claims 1-8 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of SEQ ID NOS: 88-93 which are modified recombinant proteins derived from SEQ ID NO: 87 (Phl p 5b) and pharmaceutical compositions thereof for *in vitro* diagnosis of type I allergies and *in vivo* hyposensitization to modified SEQ ID NO: 87.

Applicant is not in possession of any other modified recombinant allergen, any other modified recombinant allergen of any group wherein at least one of regions 16-42, 135-149, and 180-206, or a combination thereof are not modified, or any pharmaceutical composition thereof for any *in vitro* diagnosis of type I allergies or any *in vivo* use

Applicant has disclosed a limited number of species; therefore, the skilled artisan cannot envision all the contemplated amino acid sequence possibilities recited in the instant claims. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

The specification fails to define all modified recombinant allergens. The lack of sufficient limitations would therefore allow for all other modified recombinant allergens. Therefore, the skilled artisan cannot envision all the contemplated modified recombinant allergen possibilities recited in the instant claims. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. A description of a genus of polypeptide sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

***Claim Rejections - 35 USC § 102***

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 1-2, 4-5, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 91/06571 (IDS reference AM).

WO 91/06571 teaches recombinantly modified allergens by substitution, deletion, or addition of amino acids, and therapeutic compositions thereof (see page 3, paragraph 3 and the claims in particular). Claim 2 is included, because the feline protein is inherently one of the 6 main groups of allergens.

Therefore, WO 91/06571 anticipates the claimed invention.

20. Claims 1-5, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Smith et al. (*Molecular Immunology* 1996; 33(4/5): 399-405).

Smith et al. teach allergens modified by site-directed mutagenesis (e.g. recombinant engineering by substitution), and reduced IgE binding to the allergen variants (see the entire document; page 400, right column; and Figures 5 and 6 in particular). Additionally, "15-25% of humans are naturally sensitized to common environmental antigens and produce specific IgE" and IgG Ab (see page 399, left column in particular). Pharmaceutical compositions comprising the modified allergens were made in a physiologically harmless salt (i.e. saline) for treating IgE-mediated allergies (see page 401, left column in particular). Smith et al. teach that the advantage to peptide-based therapy is that peptides can be chemically produced in large quantities, are predicted to cause a lower frequency of adverse reaction, and provide an alternative therapy approach (see page 404, right column in particular). Claim 3 is included because Smith et al. teaches that inhalant allergens are an important group of antigens and include common environmental antigens (e.g grass pollen; see page 399, left column in particular).

Therefore, the Smith et al. reference anticipates the claimed invention.

***Claim Rejections - 35 USC § 103***

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

22. Claims 1-6, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maasch et al. (*Clinical Rev. Allergy*, 1987; 5:89-106) in view of Smith et al. (*Molecular Immunology* 1996; 33(4/5): 399-405) or WO 91/06571.

Maasch et al. teach standardized extracts and modified allergens (i.e. allergoids) "in order to reduce or abolish its native allergenic reactivity while largely retaining its native capacity to produce blocking antibodies that are able to cross-react with and neutralize the native antigens"; further, they determine that the best immunogens were "fresh extracts" (see page 89 in particular). Significant IgG responses and decreased histamine release were observed following treatment with allergoids (see pages 96 and 101 in particular). The allergoids can be given about 50 times more allergoid than standard antigen, which provides an approach to allergy immunotherapy (see page 103 in particular). Claims 2-3 and 6 are included because the allergoids taught by Maasch et al. are inherently one of groups 1-6, and Maasch et al. teach modification of grass pollen allergens, which is part of group 5 (see page 90 in particular)

Maasch et al. do not teach allergens modified by genetic engineering (e.g. recombinant).

Smith et al. and WO 91/06571 have been discussed supra.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinantly modified antigens taught by Smith et al. or WO 91/06571 for the modified allergen extracts taught by Maasch et al. because both approaches result in decreased IgE responses, while largely retaining its native capacity to produce blocking antibodies that are able to cross-react with and neutralize the native antigens as taught by Maasch et al.

One of ordinary skill in the art would have been motivated to substitute the recombinantly modified proteins taught by Smith et al. or WO 91/06571 for the allergoids taught by Maasch et al. because the recombinant process produces large quantities of peptide which cause a lower frequency of adverse reaction for immunotherapy as taught by Smith et al. or WO 91/06571.

23. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Maasch et al. (*Clinical Rev. Allergy*, 1987; 5:89-106) in view of Smith et al. (*Molecular Immunology* 1996; 33(4/5): 399-405) or WO 91/06571as applied to claims 1-6 and 11 above, and further in view of Vrtala et al. (J. Immunol, 1993; 151(9): 4773-4781) or Bufe et al. (FEBS Letters 1995; 363: 6-12).

Maasch et al., Smith et al., and WO 91/06571 have been discussed supra.

The combined reference teachings do not teach *Phl p* 5b as the allergen.

Vrtala et al. teach that type I allergic reactions represent a health problem of increasing importance, and symptoms in up to 20% of the population are caused by airborne allergens, such as plant pollens (e.g. grass; see page 4773, left column in particular). Vrtala et al. further teach a recombinant *Phl p* V allergen, a major grass pollen, which bound to IgE and has potential for therapeutic purposes for hyposensitization treatment (see the Materials and Methods, Figure 1, and the Discussion in particular). Further, Vrtala et al. teach several isoforms of *Phl p* V (see figure 2 in particular).

Bufe et al. teach major grass pollen allergens induce allergic responses in more than 90% of grass pollen allergic and nearly 40% of all Type-I allergic patients. Bufe et al. teach a recombinant cDNA encoding for the major group V allergen *Phl p* Vb, which is a pollen RNase (see the entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the recombinant *Phl p* Vb proteins taught by Vrtala et al. and Bufe et al. for the recombinantly modified allergens taught by Smith et al. or WO 91/06571 which could be obtained by extracts or modified as taught by Maasch et al. to obtain a recombinantly modified *Phl p* Vb compound and/or composition.

One of ordinary skill in the art would have been motivated to substitute the recombinant *Phl p* Vb proteins taught by Vrtala et al. and Bufe et al. for the modified allergens taught by Smith et al. or WO 91/06571 and Maasch et al. because grass pollen allergens induce allergic responses in more than 90% of grass pollen allergic and nearly 40% of all Type-I allergic patients as taught by Vrtala et al., and therefore, present a

large patient population which would benefit from treatment with the modified allergens as taught by Smith et al.

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Megan Jamroz, whose telephone number is (703) 308-8365. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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